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Ventricular volume asymmetry as a risk marker for heart failure and all-cause mortality in transfusion-dependent thalassemia

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Abstract

Aim: We measured the left-to-right ventricular volume ratio (LRVR) in a large cohort of patients with

transfusion-dependent thalassemia (TDT) and assessed its cross-sectional correlations and its prognostic value in predicting heart failure (HF) and all-cause mortality.

Methods: 1,481 TDT patients underwent cardiovascular magnetic resonance for assessment of biventricular volumes and ejection fractions (cine images) and myocardial iron overload (T2* technique) and for detection of replacement myocardial fibrosis (late gadolinium enhancement-LGE images). The LRVR was defined as the ratio between the left ventricular (LV) and right ventricular (RV) end-diastolic volume indexes.

Results: 1160 (78.3%) patients had normal ventricular symmetry, 220 (14.9%) LV dominant asymmetry (LRVR > 118%), and 101 (6.8%) RV dominant asymmetry (LRVR < 89%).

Cardiac iron levels and LGE were comparable among the three groups. LV dominance was associated with reduced LV function. RV dominance was correlated with aging, reduced RV function, and a history of arrhythmias.

The mean follow-up time was 4.82 ± 2.06 years. HF death occurred in 15 (1.01%) patients. The risk for HF death was significantly higher in the group with RV dominant asymmetry compared to that with normal ventricular symmetry (hazard ratio, HR = 6.07). All-cause death occurred in 42 (2.8%) patients. RV dominant asymmetry was associated with a significantly increased risk of all-cause mortality compared to normal ventricular symmetry [hazard ratios (HR) = 3.57] and LV dominant asymmetry (HR = 6.17). RV dominance remained associated with an increased risk of HF and all-cause mortality even after adjusting for other risk factors such as cardiac iron, LGE, or biventricular ejection fractions.

Conclusion: The LRVR may play a significant role in enhancing death risk stratification in TDT.

Keywords: Transfusion-dependent thalassemia, left-to-right ventricular volume ratio, cardiac magnetic resonance, heart failure mortality, all-cause mortality

INTRODUCTION

Transfusion-dependent beta-thalassemia (β-TDT) is a severe autosomal recessive hemoglobinopathy characterized by the absence or marked reduction of the β-globin chain synthesis. The resultant chronic hemolysis and severe anemia necessitate lifelong, regular blood transfusions, which, although essential for survival, impose a significant risk of systemic iron overload[1,2]. Due to the lack of a physiological pathway for iron excretion, excess iron progressively accumulates in parenchymal tissues, particularly the myocardium, liver, and endocrine glands, leading to end-organ damage[3-5]. Iron-induced heart failure (HF) remains the principal cause of mortality in TDT patients, although the implementation of the T2* cardiovascular magnetic resonance (CMR) has dramatically improved outcomes and survival[6,7]. Indeed, by opening the door to the non-invasive, accurate, and reproducible quantification of cardiac iron levels[8,9], the T2* CMR technique enabled precise cardiac risk stratification[10,11] and the development and assessment of the efficacy of patient-specific iron chelation regimens[12-14]. However, additional factors, such as chronic anemia, myocarditis, endocrine dysfunction, and genetic predispositions, also play significant roles in the pathophysiology of cardiovascular morbidity in TDT patients[11,15-19]. Chronic anemia leads to a compensatory high-output cardiac state. Over time, this increased workload on the heart can lead to volume overload and maladaptive cardiac remodeling. This includes dilation of the heart chambers and hypertrophy of the ventricular walls, both of which increase the risk of heart dysfunction, heart failure, and arrhythmias[20-22].

CMR also plays a crucial role in detecting early signs of ventricular remodeling, being the gold standard for quantifying biventricular volumes, myocardial mass, and systolic function via cine imaging[23-25]. A large

multicentre study employing a multiparametric CMR approach demonstrated that not only myocardial iron overload but also other CMR parameters, including ventricular dilatation and ventricular dysfunction, were linked to a higher likelihood of mortality due to heart failure[26].

Few recent studies conducted in selected non-thalassemic disease conditions suggested that, beyond the absolute size of the ventricles, the relative size between the left and right ventricles can also provide valuable insights and serve as an important marker for predicting future cardiovascular risk[27-30]. The ventricular asymmetry can be assessed through simple volume ratio assessment. An asymmetric increase in the size of one ventricle may reflect early alterations in cardiac structure and function not evident from absolute size measurements alone and may suggest an imbalance in the distribution of the cardiac workload. Anyway, the evaluation of the ventricular asymmetry is generally performed only in specific clinical scenarios where the right ventricle is primarily affected, such as for differentiating physiological adaptations (athlete's heart) from pathological conditions such as arrhythmogenic right ventricular cardiomyopathy[31].

In this study, the left-to-right ventricular volume ratio was measured in a large cohort of TDT patients with the aims of assessing its cross-sectional correlation with demographic, clinical, and CMR findings and determining its prognostic role for HF mortality or all-cause mortality.

METHODS

Study population

We considered 1,481 TDT patients consecutively enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) project. The MIOT project was an Italian network constituted by 70 thalassemia centers and 10 validated magnetic resonance imaging (MRI) centers that employed standardized protocols for MRI image acquisition and analysis[32,33]. At the baseline MRI, patients' demographics, clinical features, laboratory, and instrumental findings were recorded in a web-based database, with updates conducted at each MRI scan, scheduled according to protocol every 18 ± 3 months.

Moreover, we included 91 healthy subjects (44.50 ± 13.65 years; 50.5% females) who were part of a multicenter cohort used to establish reference values for cardiac functional parameters and myocardial T1 mapping. Healthy subjects were recruited from hospital staff, their family members, and via word of mouth and fulfilled the following inclusion criteria: normal electrocardiogram, no history of cardiac diseases or symptoms, no cardiovascular risk factors, no known systemic illnesses, and no absolute contraindications to the MRI.

All patients and healthy subjects gave informed consent in compliance with the Declaration of Helsinki. The study received approval from the institutional ethics committee.

MRI

The MRI scans were performed using 1.5T scanners of three main vendors (GE Healthcare, Milwaukee, WI; Philips, Best, Netherlands; Siemens, Erlangen, Germany) equipped with phased-array coils. Images were acquired during breath-holds with electrocardiogram (ECG) gating.

Cine images in standard long-axis and short-axis views from the atrioventricular ring to the cardiac apex were acquired using a balanced steady-state free precession (SSFP) sequence and were analyzed offline in a standard way to assess biventricular function parameters[34]. The inter-center reproducibility for the quantification of cardiac function had been previously reported[35]. Biventricular volumes and left ventricular (LV) mass were indexed to body surface area. The left-to-right ventricular volume ratio was

defined as the ratio between the LV end-diastolic volume index (EDVI) and right ventricular (RV) EDVI.

To evaluate iron overload, T2* gradient-echo multi-echo sequences were acquired. Basal, medium, and apical short-axis slices of the left ventricle[36] and a mid-hepatic slice were obtained[37]. Analysis of T2* images was conducted by experienced MRI operators (over 10 years of expertise) using HIPPOMIOT®, a custom-developed and validated software. This software calculated T2* values for all 16 LV segments based on the standard American Heart Association (AHA)/American College of Cardiology (ACC) model[38], and the global heart T2* value was determined by averaging the segmental values. Hepatic T2* values were measured within a circular region of interest, defined in a homogeneous area of parenchyma without blood vessels[37], and were converted into liver iron concentration (LIC)[39,40]. Previous studies have demonstrated both good intra- and inter-operator reproducibility and transferability across MIOT MRI centers[33].

Late gadolinium enhancement (LGE) images in both short- and long-axis views were obtained 8 min to 18 min following intravenous administration of Gadobutrol (Gadovist®; Bayer; Berlin, Germany) at the standard dose of 0.2 mmol/kg using a T1-weighted fast gradient-echo inversion recovery sequence, with inversion time individually adjusted to optimize nulling of apparently normal myocardium. LGE was considered present upon identification of hyperintense regions confirmed on two orthogonal imaging planes[18]. LGE sequences were omitted in patients with a glomerular filtration rate < 30 mL/min/1.73 m^2 and in patients who declined the administration of the contrast agent.

Diagnostic criteria

The healthy population was employed to establish the reference range for the left-to-right ventricular volume ratio. Lower and upper limits of normal were defined as the 5th and the 95th percentile values, respectively. Deviations beyond this range were classified into two distinct patterns of ventricular asymmetry: "LV dominant", characterized by a disproportionately larger left ventricle (left-to-right ventricular volume ratio > upper limit), and "RV dominant", defined by a significantly larger right ventricle (left-to-right ventricular volume ratio < lower limit).

A global heart T2* < 20 ms was considered indicative of significant myocardial iron overload (MIO)[8]. A LIC ≥ 3 mg/g/dw indicated significant hepatic iron overload[41].

Heart failure was identified based on symptoms, signs, biomarkers, and instrumental parameters, according to the current guidelines[42]. Arrhythmias were diagnosed when documented by standard ECG or 24 h Holter ECG and required specific pharmacological treatment. Classification of arrhythmias followed the AHA/ACC guidelines[43]. Pulmonary hypertension (PH) was defined by a trans-tricuspidal velocity jet exceeding 3.2 m/s[44], accompanied by corresponding signs and symptoms.

Follow-up

The end of follow-up was defined as the date of the last available MRI. For patients who did not undergo a control MRI, clinical outcomes from the baseline MRI until September 2018 were documented by the treating hematologist via a case report form. In patients who died during the study period, follow-up was censored at the date of death.

Mortality outcomes included HF mortality and all-cause mortality.

Statistical analysis

All data were analyzed using SPSS version 27.0 statistical package (IBM Corp, Armonk, NY).

Continuous variables were summarized as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages.

The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables.

Correlation analyses were performed using Pearson's test or Spearman's test as appropriate with respect to data distribution.

For continuous variables demonstrating normality, intergroup comparisons were conducted using the independent-samples *t*-test for two-group analyses, and one-way analysis of variance (ANOVA) for comparisons involving more than two groups. For continuous variables with non-normal distributions, comparisons between two groups were performed using the Mann-Whitney *U* test, while comparisons involving more than two groups utilized the Kruskal-Wallis test. Differences in categorical variables were tested using Chi-square or Fisher's exact test. The Bonferroni correction was used for multiple comparisons.

The analysis of covariance (ANCOVA) was used to evaluate whether between-group differences persisted after controlling for potential covariates. Covariates were included if they significantly differed between groups and were associated with the considered dependent variable. When necessary, variables were log-transformed to normalize the residual distributions and to equalize the residual variance.

The Cox regression was applied to evaluate the relationship between the selected prognostic variables and the outcome. Results were expressed as hazard ratios (HR) along with 95% confidence intervals (CI). Kaplan-Meier curves were generated to estimate survival. The log-rank test was used to compare survival curves between groups.

A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Left-to-right ventricular volume ratio in healthy subjects

In the healthy population, the mean left-to-right ventricular volume ratio was 101.85 ± 8.16%. It was comparable between males and females (100.37 ± 7.93% *vs.* 103.29 ± 8.20%; $P = 0.068$) and was not correlated with age (R = 0.235; $P = 0.085$).

The lower and upper limits of the left-to-right ventricular volume ratio were 89% and 118%, respectively.

Patients' characteristics

All TDT patients were white and well distributed between males ($N = 711$; 48.0%) and females ($N = 770$; 52.0%). The mean age at the baseline CMR was 31.03 ± 8.86 years. All patients were regularly transfused since early childhood and chelated. Patients started chelation therapy in the mid-to-late 1970s, while patients born after this era commenced chelation treatment during early childhood. Chelation regimens were individualized and prescribed in accordance with current evidence-based clinical guidelines, guided by comprehensive clinical evaluation, laboratory parameters, and instrumental assessments.

The mean left-to-right ventricular volume ratio was 105.82 ± 13.98% (range: 39.47%-208.51%). Overall, 1160 (78.3%) patients had normal ventricular symmetry, 220 (14.9%) patients had LV dominant asymmetry, and 101 (6.8%) patients had RV dominant asymmetry.

Associations of ventricular asymmetry with demographic, clinical, and CMR findings

Table 1 shows the comparison of demographic, clinical, and CMR characteristics among the three groups of TDT patients identified according to the ventricular symmetry.

No significant differences were found in terms of sex, age at the start of regular transfusions, and serum levels of pre-transfusion hemoglobin and ferritin. Age was significantly different among the three groups, with TDT patients with RV dominant asymmetry being older than both patients with normal ventricular symmetry ($P < 0.0001$) and with LV dominant asymmetry ($P < 0.0001$).

TDT patients with RV dominant asymmetry had an increased prevalence of pre-existing arrhythmias compared to the group with normal ventricular symmetry ($P = 0.015$). Among the arrhythmias, the supraventricular arrhythmias (atrial fibrillation and atrial flutter) were the most common type (79%).

Cardiac and hepatic iron levels were comparable among the three groups.

The LV EDVI was not significantly different between patients with normal ventricular symmetry and patients with LV dominant asymmetry, while both groups exhibited a significantly increased LV EDVI compared to patients with RV dominant asymmetry ($P < 0.0001$ for both comparisons). The group with LV dominant asymmetry had a worse LV ejection fraction (EF) compared to both groups with normal ventricular symmetry and RV dominant asymmetry ($P < 0.0001$ for both comparisons).

The RV EDVI was significantly higher in both groups with normal ventricular asymmetry and RV dominant asymmetry compared to the group with LV dominant asymmetry ($P < 0.0001$ for both comparisons) and in the group with RV dominant asymmetry compared to the group with normal ventricular symmetry ($P = 0.015$). The group with RV dominant asymmetry had a worse RV EF compared to both groups with normal ventricular symmetry and LV dominant asymmetry ($P < 0.0001$ for both comparisons). All the between-group differences in LV and RV EDVI remained significant in the ANCOVA model after adjustment for age. The LV mass index was comparable among the three groups.

The contrast medium was injected in 1,183 (79.9%) patients, and 201 (17.0%) of them showed replacement myocardial fibrosis. Only two patients exhibited a transmural pattern of LGE, whereas the remaining patients demonstrated a non-ischemic LGE pattern. A total of 61.0% of patients presented with at least two distinct foci of myocardial fibrosis. The prevalence of replacement myocardial fibrosis did not differ significantly among the three TDT subgroups stratified by ventricular symmetry.

Patient outcomes

The mean follow-up time was 4.82 ± 2.06 years (median: 5.01 years).

All-cause death occurred in 42 (2.8%) patients. Specifically, 15 (35.7%) patients died for HF, 7 (16.7%) patients for cancer, 4 (9.5%) patients for cirrhosis, 4 (9.5%) patients for myocardial infarction, 3 (7.1%) patients for sepsis, 2 (4.8%) patients for anaphylactic shock, 2 (4.8%) patients for bone marrow transplant complications, 1 (2.4%) patient for pneumonia, 1 (2.4%) patient for agranulocytosis, 1 (2.4%) patient for trauma, 1 (2.4%) patient for suicide, and 1 (2.4%) patient for an unknown cause.

Table 1. Baseline demographic, clinical, and MRI data of the three groups identified based on the left-to-right ventricular volume ratio

Variable	Normal asymmetry (*N* = 1,160)	LV dominant asymmetry (*N* = 220)	RV dominant asymmetry (*N* = 101)	*P*-value
Females, *N* (%)	599 (51.6)	125 (56.8)	46 (45.5)	0.150
Age (years)	30.74 ± 8.78	30.73 ± 9.54	34.98 ± 7.28	< 0.0001
Age at the start of regular transfusions (years)	1.59 ± 1.23	1.57 ± 1.19	1.46 ± 1.19	0.458
Pre-transfusion hemoglobin (g/dL)	9.60 ± 0.67	9.56 ± 0.77	9.54 ± 0.44	0.453
Serum ferritin (ng/L)	1,460.46 ± 1,403.86	1,674.35 ± 1,652.84	1,414.04 ± 1,700.32	0.058
History of HF, *N* (%)	62 (5.3)	14 (6.4)	11 (10.9)	0.071
History of arrhythmias, *N* (%)	67 (5.8)	12 (5.5)	13 (12.9)	0.016
History of pulmonary hypertension, *N* (%)	14 (1.2)	1 (0.5)	3 (3.0)	0.161
Global heart T2* (ms)	29.26 ± 11.98	28.09 ± 13.25	30.01 ± 11.97	0.225
Significant MIO, *N* (%)	298 (25.7)	71 (32.3)	28 (27.7)	0.127
Number of segments with T2* < 20 ms	4.52 ± 6.12	5.35 ± 6.60	4.47 ± 5.96	0.513
MRI LIC (mg/g/dw)	8.74 ± 10.58	9.64 ± 10.95	9.18 ± 13.33	0.218
Hepatic iron overload, *N* (%)	737 (63.5)	145 (65.9)	58 (57.4)	0.340
LV EDVI (mL/m^2)	87.51 ± 18.75	89.62 ± 18.09	75.94 ± 19.17	< 0.0001
LV mass index (g/m^2)	57.84 ± 12.87	59.17 ± 16.04	60.22 ± 15.84	0.476
LV EF (%)	61.98 ± 6.95	57.49 ± 7.44	62.63 ± 9.27	< 0.0001
RV EDVI (mL/m^2)	84.88 ± 18.17	69.80 ± 15.40	93.75 ± 34.44	< 0.0001
RV EF (%)	61.57 ± 7.64	61.26 ± 9.44	53.81 ± 9.07	< 0.0001
Replacement myocardial fibrosis, *N* (%)	159/932 (17.1)	27/164 (16.5)	15/87 (17.2)	0.980

N: Number; LV: left ventricular; RV: right ventricular; HF: heart failure; MIO: myocardial iron overload; MRI: magnetic resonance imaging; LIC: liver iron concentration; EDVI: end-diastolic volume index; EF: ejection fraction; MRI: magnetic resonance imaging.

The most frequent type of HF was HF with reduced ejection fraction (11/15 deaths = 73.3%). Most of the patients with HF with reduced ejection fraction presented to healthcare providers with decreased exercise tolerance, primarily due to dyspnea and/or fatigue. Two patients developed chronic heart failure diagnosed more than one year after the CMR scan and both experienced rapid clinical deterioration. One patient had heart failure with preserved ejection fraction (HFpEF) and showed evidence of underlying structural heart disease.

The mean time from the baseline MRI to the HF-related death was 2.06 ± 2.02 years and 7 (46.7%) deaths occurred within the first year of follow-up.

Association between ventricular symmetry and heart failure mortality

The prevalence of HF death was 0.7% for patients with normal ventricular symmetry, 1.4% for patients with LV dominant asymmetry, and 4.0% for patients with dominant RV asymmetry, with a significant difference between patients with normal ventricular symmetry and RV dominant asymmetry ($P = 0.036$).

Table 2 shows the results of the univariate Cox Regression analysis for the prediction of HF mortality.

HF mortality was not associated with age, gender, hepatic iron levels, or pre-transfusion hemoglobin. Compared to the group with normal ventricular symmetry, only the group with RV dominant asymmetry was associated with a significantly increased risk of HF mortality. The RV dominant asymmetry did not provide additional prognostic stratification in comparison to the LV dominant asymmetry (HR = 2.69, 95%CI = 0.59-12.04, $P = 0.197$). The Kaplan-Meier curve showing the impact of the ventricular symmetry on

Table 2. Univariate Cox regression for the prediction of heart failure mortality

	N (%) in group	*N* (%) of HF deaths	Univariate analysis	
			HR (95%CI)	*P*-value
Sex				
Male	711 (48.0)	9 (1.3)	Reference	
Female	770 (52.0)	6 (0.8)	0.61 (0.22-1.72)	0.351
Age			1.05 (0.99-1.12)	0.102
Age at the start of regular transfusions			0.90 (0.54-1.49)	0.686
Pre-transfusion hemoglobin			0.42 (0.17-1.03)	0.058
Serum ferritin			1.00 (1.00-1.01)	< 0.0001
History of HF				
No	1394 (94.1)	12 (0.9)	Reference	
Yes	87 (5.9)	3 (3.4)	4.03 (1.14-14.29)	0.031
History of arrhythmias				
No	1389 (93.8)	12 (0.9)	Reference	
Yes	92 (6.2)	3 (3.3)	3.89 (1.09-13.80)	0.035
Hepatic iron overload				
No	541 (36.5)	3 (0.6)	Reference	
Yes	940 (63.5)	12 (1.3)	2.30 (0.65-8.16)	0.196
Significant MIO				
No	1084 (73.2)	7 (0.6)	Reference	
Yes	397 (26.8)	8 (2.0)	3.09 (1.12-8.53)	0.029
LV EF			0.89 (0.85-0.93)	< 0.0001
RV EF			0.92 (0.89-0.95)	< 0.0001
Myocardial fibrosis (*N* = 1,183)				
No	982 (83.0)	8 (0.8)	Reference	
Yes	201 (17.0)	6 (3.0)	3.73 (1.29-10.75)	0.015
Ventricular symmetry				
normal	1160 (78.3)	8 (0.7)	Reference	
LV dominant	220 (14.9)	3 (1.4)	2.17 (0.58-8.22)	0.251
RV dominant	101 (6.8)	4 (4.0)	6.07 (1.83-20.18)	0.003

N: Number; HF:heart failure; HR: hazard ratio; CI: confidence intervals; MIO: myocardial iron overload; LV: left ventricular; EF: ejection fraction; RV: right ventricular; MRI: magnetic resonance imaging.

HF mortality is shown in Figure 1A. The log-rank test revealed a significant difference in the curves (P = 0.004). The other univariate prognosticators of HF mortality were mean serum ferritin levels, history of HF and arrhythmias, significant myocardial iron overload, LV and RV ejection fractions, and replacement myocardial fibrosis.

The low number of deaths for HF prevented performing a multivariate analysis including simultaneously all univariate prognosticators. Different Cox regression analyses were performed, adjusting the ventricular symmetry for one univariate prognosticator at a time [Table 3]. In all tested models, RV dominance remained associated with an increased risk for HF mortality.

Association between ventricular symmetry and all-cause mortality

Patients with RV dominant asymmetry had a significantly higher all-cause mortality rate compared to both patients with normal ventricular symmetry (8.9% *vs.* 2.6%; $P < 0.0001$) and with LV dominant asymmetry (8.9% *vs.* 1.4%; $P = 0.006$).

Table 4 shows the results of the univariate Cox Regression analysis for the prediction of all-cause mortality. RV dominant asymmetry was associated with a significantly increased risk of all-cause mortality compared to normal ventricular symmetry (HR = 3.57, 95%CI = 1.69-7.53, $P = 0.001$) and to LV dominant asymmetry (HR = 6.17, 95%CI = 1.67-22.85, $P = 0.006$). The Kaplan-Meier curve showing the impact of the ventricular

Table 3. Cox regression analysis for prediction of HF death adjusted for different covariates in TDT patients stratified by ventricular symmetry

	LV asymmetry *vs.* normal ventricular symmetry		RV asymmetry *vs.* normal ventricular symmetry		RV asymmetry *vs.* LV asymmetry	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Model 1: crude	2.17 (0.58-8.22)	0.251	6.07 (1.83-20.18)	0.003	2.69 (0.59-12.04)	0.197
Model 2: adjusted for serum ferritin	2.48 (0.44-13.79)	0.301	9.56 (2.10-43.51)	0.004	3.68 (0.61-22.18)	0.154
Model 3: adjusted for history of HF	2.19 (0.58-8.26)	0.249	5.74 (1.72-19.16)	0.005	2.42 (0.54-10.94)	0.250
Model 4: adjusted for history of arrhythmias	2.18 (0.58-8.23)	0.250	5.29 (1.56-17.93)	0.007	1.99 (0.43-9.25)	0.382
Model 5: adjusted for significant MIO	2.05 (0.54-7.77)	0.290	5.98 (1.79-18.87)	0.004	3.28 (0.73-14.69)	0.178
Model 6: adjusted for LV EF	1.28 (0.33-4.96)	0.719	5.58 (1.62-19.15)	0.006	4.49 (0.99-20.49)	0.052
Model 7: adjusted for RV EF	1.94 (0.51-7.38)	0.328	1.95 (1.10-11.60)	0.050	1.59 (0.35-7.21)	0.542
Model 8: adjusted for replacement myocardial fibrosis	2.37 (0.63-8.96)	0.203	4.25 (1.13-16.03)	0.033	1.69 (0.34-8.43)	0.520

LV: Left ventricular; RV: right ventricular; HR: hazard ratio; CI: confidence intervals; HF: heart failure; MIO: myocardial iron overload; EF: ejection fraction; TDT: transfusion-dependent thalassemia.

Table 4. Univariate Cox regression for the prediction of all-cause death

	N (%) in group	N (%) of all-cause deaths	Univariate analysis	
			HR (95%CI)	p-value
Sex				
Male	711 (48.0)	25 (3.5)	Reference	
Female	770 (52.0)	17 (2.2)	0.61 (0.33-1.13)	0.116
Age			1.05 (1.02-1.09)	0.006
Age at the start of regular transfusions			1.24 (0.99-1.57)	0.063
Pre-transfusion hemoglobin			0.73 (0.44-1.21)	0.219
Serum ferritin			1.00 (1.00-1.01)	0.032
History of HF				
No	1394 (94.1)	30 (2.2)	Reference	
Yes	87 (5.9)	12 (13.8)	6.51 (3.33-12.73)	< 0.0001
History of arrhythmias				
No	1389 (93.8)	30 (2.2)	Reference	
Yes	92 (6.2)	12 (13.0)	6.35 (3.25-12.41)	< 0.0001
Hepatic iron overload				
No	541 (36.5)	13 (2.4)	Reference	
Yes	940 (63.5)	29 (3.1)	1.30 (0.68-2.51)	0.429
Significant MIO				
No	1084 (73.2)	23 (2.1)	Reference	
Yes	397 (26.8)	19 (4.8)	2.39 (1.29-4.39)	0.005
LV EF			0.93 (0.89-0.96)	< 0.0001
RV EF			0.93 (0.91-0.95)	< 0.0001
Myocardial fibrosis (N = 1,183)				
No	982 (83.0)	24 (2.4)	Reference	
Yes	201 (17.0)	8 (4.0)	1.68 (0.75-3.74)	0.205
Ventricular symmetry				
Normal	1160 (78.3)	30 (2.6)	Reference	
LV dominant	220 (14.9)	3 (1.4)	0.59 (0.18-1.92)	0.378
RV dominant	101 (6.8)	9 (8.9)	3.57 (1.69-7.53)	0.001

N: Number; HR: hazard ratio; CI: confidence intervals; HF: heart failure; MIO: myocardial iron overload; LV: left ventricular; EF: ejection fraction; RV: right ventricular.

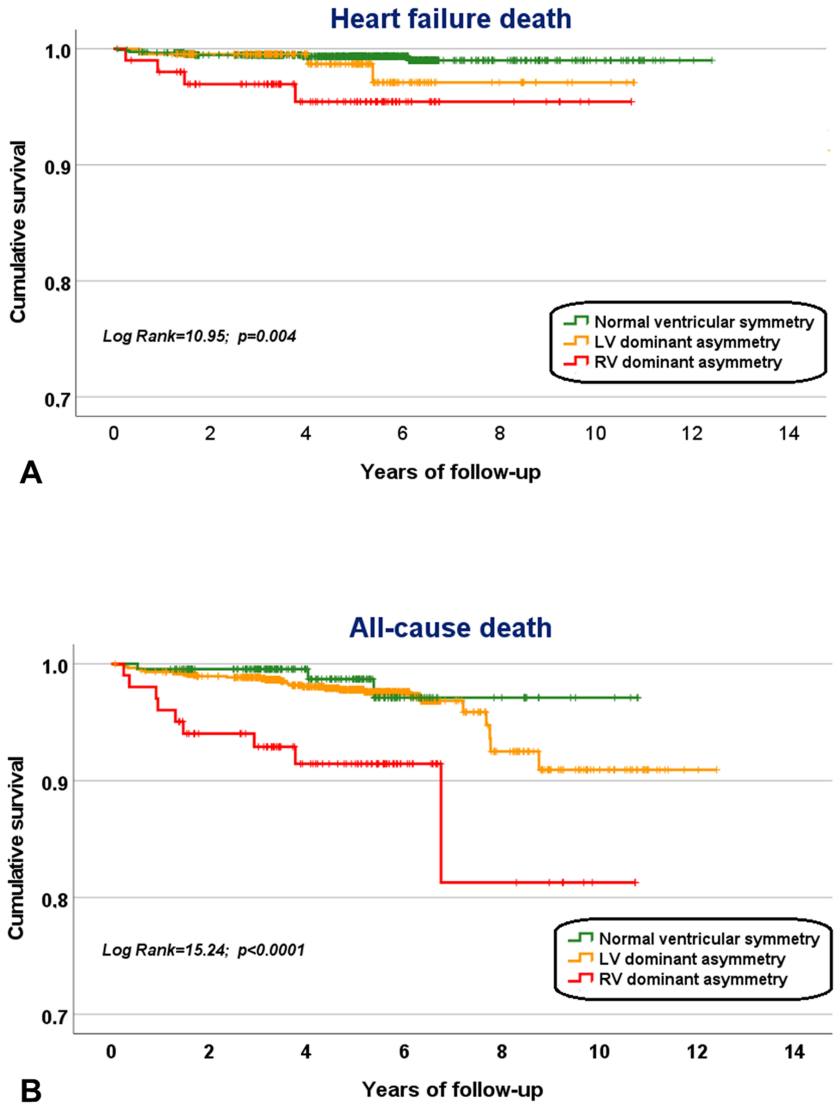

Figure 1. Kaplan-Meier curve of heart failure death (A) and all-cause death (B) according to baseline ventricular symmetry.

symmetry on all-cause mortality is shown in Figure 1B. The log-rank test revealed a significant difference in the curves ($P < 0.0001$). The other univariate prognosticators of all-cause mortality were age, serum ferritin levels, history of HF and arrhythmias, significant MIO, and LV and RV ejection fractions.

Different Cox regression analyses were performed, adjusting the ventricular symmetry for a group of univariate prognosticators at a time [Table 5]. In all tested models, RV dominance remained associated with an increased risk for all-cause death compared to both normal ventricular symmetry and LV dominance.

DISCUSSION

The left-to-right ventricular volume ratio can be easily derived from routinely available CMR parameters; however, its clinical relevance has been poorly investigated. This is the first study to evaluate this metric in TDT.

Table 5. Cox regression analysis for prediction of all-cause death adjusted for different covariates in TDT patients stratified by ventricular symmetry

	LV asymmetry *vs.* normal ventricular symmetry		RV asymmetry *vs.* normal ventricular symmetry		RV asymmetry *vs.* LV asymmetry	
	HR (95%CI)	***P*-value**	**HR (95%CI)**	***P*-value**	**HR (95%CI)**	***P*-value**
Model 1: crude	0.59 (0.18-1.92)	0.378	3.57 (1.69-7.53)	0.001	6.17 (1.67-22.85)	0.006
Model 2: adjusted for age and serum ferritin	0.45 (0.11-1.92)	0.280	3.06 (1.36-6.91)	0.007	8.22 (1.71-39.55)	0.009
Model 3: adjusted for history of heart failure and arrhythmias	0.61 (0.19-2.01)	0.421	2.99 (1.41-6.35)	0.004	4.61 (1.23-17.25)	0.023
Model 5: adjusted for CMR predictors (significant MIO, LV EF, and RV EF)	0.47 (0.14-1.58)	0.224	2.77 (1.25-6.14)	0.012	5.44 (1.24-23.82)	0.025

LV: Left ventricular; RV: right ventricular; HR: hazard ratio; CI: confidence intervals; HF: heart failure; MIO: myocardial iron overload; EF: ejection fraction; TDT: transfusion-dependent thalassemia.

To define the normal range for the left-to-right ventricular volume ratio, we included in our study a group of healthy subjects free from cardiovascular risk factors and cardiac or systemic diseases. The identified normal range (between 89% and 118%) is quite consistent with that identified in a previous study (between 80 and 112%), where the group of subjects was significantly larger, but the presence of cardiovascular risk factors, such as diabetes, obesity, hypertension, and smoking, did not represent one of the exclusion criteria[29].

Almost three-quarters of TDT patients had balanced LV and right ventricular volumes, while the prevalence of LV dominance was almost double compared to RV dominance. In line with a UK study involving 44,796 patients affected by different cardiac and respiratory diseases[29] and another study focused on patients with heart failure with preserved ejection fraction[27], we confirmed in TDT patients the lack of an association of LV dominant asymmetry with aging, gender, and LGE and the presence of a link between LV dominance and reduced LV systolic function. Conversely, we failed to detect a link between LV dominant asymmetry and increased LV mass index. The pathway linking LV dominant asymmetry to LV hypertrophy is complex[29], and in TDT, it is further complicated by the presence of many other drivers of LV hypertrophy, including volume overload and myocardial siderosis[45,46].

The RV dominant asymmetry showed a correlation with aging and reduced RV function. The absence of a link between RV asymmetry and pulmonary hypertension is most likely due to the low number of patients with the disease, thanks to the good transfusional regimen, able to reduce both the chronic hemolysis and its negative effects on nitric oxide availability and the circulating proinflammatory hormones[47,48]. Conversely, we demonstrated an association between RV dominant asymmetry and a history of arrhythmias (mainly supraventricular). Studies specifically reporting the prevalence and clinical significance of adverse cardiac outcomes of RV involvement in TDT are lacking. This gap likely reflects the historical underappreciation of the RV and its ability to predict cardiac outcomes, despite its now recognized independent and additive value beyond left ventricular function. Indeed, in other populations, a link between atrial fibrillation and right ventricular dilatation and/or dysfunction has been demonstrated[49,50].

In the prospective part of our study, we explored the prognostic ability of the left-to-right ventricular volume ratio with respect to HF mortality and all-cause mortality. Our results demonstrated that TDT patients with RV dominance had a significantly increased risk of heart failure death as well as all-cause death compared with those with normal ventricular symmetry. Moreover, the RV dominance was associated with an increased all-cause mortality risk in comparison to the LV dominance. Importantly, the

prognostic significance remained even after adjustment for other significant univariate prognosticators, including myocardial iron overload and LGE, which are well-established biomarkers for unfavorable prognosis[10,11,51].

Previous studies using CMR or other non-invasive imaging modalities like computed tomography have demonstrated the value of RV dominance as a mortality risk marker in different clinical settings, including patients without selected cardiac diseases[29], heart failure with preserved ejection fraction[27], pulmonary hypertension[52], interstitial lung disease[53], and pulmonary embolism[54]. Of note, in some cases, metrics different from the left-to-right ventricular volume ratio, such as the ratio between RV and LV diameters or volumes, have been used to assess the ventricular symmetry. Our study corroborates the literature and expands upon it by demonstrating that the connection between RV asymmetry and increased HF or all-cause mortality is also present within the unique pathophysiological landscape of TDT.

The RV and LV are intricately linked through the interventricular septum, shared epicardial circumferential myocyte fibers, and the surrounding pericardium, collectively establishing the foundation of ventricular interdependence[55]. So, the volume ratio provides a more comprehensive perspective on cardiac adaptation to pathological conditions. In the setting of chronic RV volume overload, the septum can shift toward the LV, leading to a reduction in LV capacity and impairing its function[56]. Under such conditions, an elevated volume ratio reflects not only the anatomical remodeling and enlargement of the right ventricle but also highlights the pathophysiological disruption of ventricular harmony and coordinated function.

Recent findings suggest that RV remodeling may also reflect broader systemic or non-cardiac processes that contribute to elevated all-cause mortality. Indeed, systemic conditions such as renal dysfunction[57], liver disease[58], and cancer[59] have been associated with adverse RV remodeling. Furthermore, biological processes such as chronic inflammation, oxidative stress, and fibrosis are strongly linked to RV remodeling[60,61] and may contribute to increased all-cause mortality. This evolving understanding positions RV remodeling as a potential surrogate marker for complex pathophysiological processes that extend beyond the cardiovascular system.

The recognition of RV remodeling as a clinical biomarker of systemic physiological strain highlights the need for comprehensive, multidisciplinary management in thalassemia. In addition to the two cornerstones of care-regular red blood cell transfusions and iron chelation therapy-the careful use of cardiopulmonary medications, when indicated, along with interventions targeting systemic contributors, may help improve RV structure and function by reducing overall physiological stress and mitigating secondary cardiac involvement.

The main limitations of our study were its retrospective design and the small number of events. The limited number of deaths prevented us from conducting a multivariate analysis including all univariate prognosticators, which may affect the strength and generalizability of our conclusions. While the observed associations appear clinically meaningful, they should be interpreted with caution and highlight the need for larger, prospective cohorts with sufficient event rates to enable more robust risk stratification and confirmatory analyses. Additionally, the small sample size restricted our ability to perform subgroup analyses, which could have provided a more nuanced understanding of the prognostic value of the left-to-right ventricular volume ratio in specific patient subgroups. We finally acknowledge that detailed data on transfusion history and transferrin saturation index were not available for inclusion in the present analysis. These parameters could have offered valuable insights into iron burden and disease progression.

Conclusion

In TDT, RV dominant asymmetry is associated with increased HF and all-cause mortality, highlighting the importance of incorporating a thorough evaluation of ventricular geometry in routine CMR assessments. Further studies are needed to evaluate the transferability of these findings to other TDT populations and to better elucidate the biological pathways and mechanisms that link ventricular asymmetry to mortality, providing insights that may guide future therapeutic approaches.

DECLARATIONS

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Authors' contributions

Study design and conception, data curation, statistical analysis, general coordination and supervision of the study, and draft manuscript writing: Meloni A

Monitoring and management of data collection, data curation, and manuscript revision: Pistoia L

Image acquisition and analysis, data collection, and manuscript revision: Restaino G, Zerbini M, Grassedonio E, Vallone A

Patients' recruitment, clinical examination, clinical data acquisition, and manuscript revision: Longo F, Borsellino Z, Lisi R, Cecinati V, Spasiano A, Rosso R

Development of the software for T2* image analysis, general coordination, and manuscript revision: Positano V

Image acquisition and analysis, data collection, general coordination and supervision of the study, and manuscript revision: Clemente A

Availability of data and materials

The data underlying this article cannot be shared publicly due to privacy reasons. The data will be shared upon reasonable request to the corresponding author.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Area Vasta Nord Ovest (protocol code 34008, date of approval 29 September 2006). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

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